Comorbidities and COPD Assessment Test (CAT) responsiveness in Acute Exacerbation of Chronic Obstructive Pulmonary Disease (COPD)

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Sob orientação de Doutor Pedro Braga Correia de Sá Leuschner

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Artigo de Investigação Médica

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Contents

Abbreviations 9
List of tables 11
List of figures 11
Abstract 13
Resumo 15
Introduction 17
Material and methods 19
Results 21
Discussion 31
Conclusion 37
References 39

Abbreviations

AECOPD	Acute Exacerbations of Chronic Obstructive Pulmonary Disease
AF	Atrial fibrillation
BMI	Body mass index
CAP	Community-acquired pneumonia
CAT	COPD Assessment Test
CI	Confidence interval
CKD	Chronic kidney disease
COPD	Chronic Obstructive Pulmonary Disease
ED	Emergency department
FEV_1	Forced expiratory volume in 1 second
FEV_1/FVC	Forced expiratory volume in 1 second/forced vital capacity;
FVC	Forced vital capacity
GERD	Gastroesophageal reflux disease
GOLD	Global Initiative for Chronic Obstructive Lung Disease
MI	Myocardial infarction
OSA	Obstructive sleep apnea
PAD	Peripheral arterial disease

List of tables

Table 1: Demographic and clinical characteristics.....22

Table 2: CAT at ED admission, CAT 30 days after hospital discharge and CAT recovery 24

Table 3: Comparison of CAT at ED admission and 30-days CAT recovery and comorbidities ...26

Table 4: Comparison of comorbidities between hospitalized and non-hospitalized patients and their relationship with the length of hospitalization 27

Table 5: Comparison of comorbidities between ED readmitted and non-readmitted patients for any cause and for AECOPD 28

Table 6: Comparison of comorbidities between rehospitalized and non-rehospitalized patients for any cause and for AECOPD.....29

Table 7: Comparison of comorbidities and fatal outcome 30

List of figures

Figure 1: Burden of comorbidities 21

Abstract

Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD) have negative impact in the course of disease. Comorbidities are frequent and play an important role in COPD. COPD Assessment Test (CAT) is responsive to interventions, such as AECOPD. The main goal of this study is to determine the role of comorbidities and CAT responsiveness in AECOPD.

This study is conducted in emergency department (ED) where a CAT was performed. Inclusion criteria: (1) > 40 years; (2) FEV_1 < 80% predicted and FEV_1/FCV < 0,70 (3) AECOPD as main diagnosis. Exclusion criteria: (1) other condition than COPD as main diagnosis; (2) unknown or inaccessible FEV_1 and/or FEV_1/FVC; (3) inability to answer CAT. Demographic and clinical data such as comorbidities were collected. Participants were prospectively followed up for 30 days. Hospitalization and the length of hospitalization, readmissions, rehospitalizations and fatality were recorded. Thirty days after discharge, a new CAT was performed.

The most common comorbidities were hypertension (64,4%), heart failure (49,6%) and dyslipidemia (47%). 63,5% were hospitalized. The length of hospitalization was 11,5±11,1 days. 30,4% were readmitted. The 30-day fatality was 3,5%. CAT recovery was 3,6±3,7 between ED admission and 30 days after discharge. Hospitalized, non-readmitted and non-rehospitalized patients had greater CAT recovery. Underweight patients and obese patients had a worse CAT recovery. Overweight patients had greater CAT recovery. Gastroesophageal reflux disease (GERD) was associated with ED readmission for AECOPD (OR 2.92; IC95% (1,14-7,47)) and with rehospitalization for AECOPD (OR 3.31; IC95% (1,06-10,38)). Cerebrovascular disease was also associated with rehospitalization for AECOPD (OR 5.23; IC 95% (1,09-24,95)) and 30-day fatality (p=0,024).

The prevalence of comorbidities is high. AECOPD is associated with a high rate of hospitalization and length of hospitalization, ED readmissions and rehospitalizations at 30 days. GERD and cerebrovascular disease increase ED readmission and rehospitalization rates; cerebrovascular disease worsens 30-day fatality. CAT score is responsive to recovery and sensitive for AECOPD relapses and other clinical entities. Body mass index is relevant in CAT score recovery.

Keywords: Chronic obstructive pulmonary disease; COPD; Acute exacerbation of COPD; comorbidities; COPD Assessment Test; CAT.

Resumo

As exacerbações agudas da doença obstrutiva crónica (EADPOC) têm impacto negativo no curso da doença. As comorbilidades são frequentes e desempenham um papel importante na DPOC. O COPD Assessment Test (CAT) é responsivo a intervenções, como à EADPOC. O objectivo principal deste estudo é determinar o papel das comorbilidades e a responsividade do CAT na EADPOC.

O estudo foi realizado no serviço de urgência onde o CAT foi realizado aos participantes. Os critérios de inclusão foram: (1) > 40 anos de idade; (2) FEV_1 < 80% valor predito e FEV_1/FCV < 0,70 (3) EADPOC como diagnostico principal. Os critérios de exclusão foram: (1) outras condições além de DPOC como dagnostico principal; (2) FEV_1 e/ou FEV_1/FVC desconhecido ou inacessivel; (3) incapacidade de responder ao CAT. Informação demográfica e clínica como as comorbilidades foi registada. Os participantes foram seguidos prospectivamente durante 30 dias. Internamento e duração do internamento, readmissões, reinternamentos e letalidade foram registados. Trinta dias depois da alta hospitalar, um novo CAT foi realizado.

As comorbilidades mais comuns foram: hipertensão (64,4%), insuficiência cardiaca (49,6%) e dislipidemia (47%). 63,5% foram internados. A duração do internamento foi 11,5±11,1 dias. A fatalidade aos 30 dias foi 3,5%. A recuperação no CAT foi 3,6±3,7 entre a admissão e 30 dias depois da alta hospitalar. Os participantes internados, os que não foram readmitidos nem reinternados mostraram uma recuperação mais acentuada no CAT. Participantes com baixo indice de massa corporal (IMC) e obesos mostraram pior recuperação. Participantes com excesso de peso mostraram melhor recuperação. Doença do refluxo gastroesofágico (DRGE) foi associada com as readmissões por EADPOC (OR 2.92; IC95% (1,14-7,47)) e com rehospitalizações por EADPOC (OR 3.31; IC95% (1,06-10,38)). Doença cerebrovascular também foi assocada a rehospitalizações por EADPOC (OR 5.23; IC 95% (1,09-24,95)) e fatalidade aos 30 dias (p=0,024).

A prevalência de comorbilidades é alta. A AEDPOC é associada a uma alta taxa de hospitalizações e duração de internamento, readmissões e rehospitalizações aos 30 dias. A DRGE e as doenças cerebrovasculares aumentam as taxas de readmissão e rehospitalização; a doença cerebrovascular piora a letalidade aos 30 dias. O CAT é responsivo à recuperação e sensivel para EADPOC recaídas e outras entidades clínicas. O IMC é relevante na recuperação do CAT.

Palavras-chave: Doença pulmonar obstrutiva crónica; DPOC; exacerbação aguda da DPOC; comorbilidades; COPD Assessment Test; CAT.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is defined as a common preventable and treatable disease that is characterized by persistent airflow limitation that is usually progressive [1].

In Europe, the prevalence of COPD is between 2% and 10% [2]. In Portugal a prevalence of 14,2% was reported [3]. COPD is the fourth leading cause of death worldwide, and it is estimated to become the third leading cause of death by 2020 [4]. It is estimated that by 2020, COPD will be the fifth most important cause of burden of disease and chronic disability [5]. In Europe, COPD is responsible for 56% of the costs of respiratory diseases and COPD exacerbations is the major contributor for the total COPD burden on the health care system [1].

Acute exacerbations of COPD (AECOPD) are major events with negative impact on the course of the disease [1]. They are associated with transient decreases in lung function that can take several weeks to recover [6]. Moreover, frequent AECOPD are associated with more rapid decline of forced expiratory volume in 1 second (FEV_1) [7]. AECOPD also negatively affect the patients' quality of life [8]. The overall exercise tolerance, physical activity [9] and the physiological wellbeing [10] are also reduced during an AECOPD. Finally, AECOPD are associated with significant mortality, especially those requiring hospitalization [11].

Several risk factors for frequent AECOPD were identified, namely increased age, severity of FEV_1 impairment, frequent past exacerbations, persistent symptoms of chronic bronchitis and comorbid conditions, mainly cardiovascular disease [12].

Comorbidities are frequent among COPD patients [1]. They play an important role in the history of the disease. Firstly, they can share similar pathophysiological mechanisms with COPD. Secondly, their impact on health status, healthcare utilization and all-cause hospital admissions is significant. Thirdly, mortality due to comorbidities can occur earlier than respiratory causes. Finally, understanding the clusters of comorbidities can have diagnostic, therapeutic and prognostic implications [2].

Classifying COPD only based on FEV_1 % of predicted is no longer adequate. Nowadays, COPD classification and management are both based on spirometric criteria and patients' health-related quality of life. COPD health status measurements, such as the St. George Respiratory Questionnaire and Chronic Respiratory Questionnaire provide this additional information but their complexity made them impractical in for use in clinical routine. Recent guidelines recommend either the modified British Medical Research Council (mMRC) dyspnoea scale or the COPD assessment test (CAT). COPD assessment test (CAT) is a simple instrument that provides information not only about the symptoms but also about the impact of COPD on wellbeing [1].

Several studies support the reliability and validity of the CAT and its responsiveness to interventions, such as pulmonary rehabilitation [13] [14] [15] and exacerbation recovery on treatment [16] [17] [14] [18] [19]. However, its validity and responsiveness need to be assessed in specific patient populations [20].

The present study had three main goals: (1) to determine the role of comorbidities on AECOPD, defining their importance on length of hospitalization and short-term emergency department readmissions, rehospitalizations and mortality; (2) to define the CAT score responsiveness to AECOPD recovery, to quantify the CAT score improvement at 30 days and to determine the role of comorbidities in this score recovery; (3) to analyze the differences in CAT score recovery 30 days after an AECOPD among readmitted or rehospitalized and non-readmitted or non-rehospitalized patients for all causes and for AECOPD.

Material and methods

Study design and setting

The present study is a longitudinal and observational study conducted from 1.September 2014 to 31. January 2015 in the emergency department (ED) of Hospital de Santo António – Centro Hospitalar do Porto, a central hospital in Porto, Portugal. The study was approved by the Ethics Committee of Centro Hospitalar do Porto. The patients participated voluntarily and written informed consent forms were obtained.

Patients

The inclusion criteria were: (1) age above 40 years; (2) Forced expiratory volume in 1 second (FEV_1) < 80% predicted and Tiffeneau index (FEV_1/FCV) < 0,70 (3) ED admission with AECOPD as main diagnosis.

The exclusion criteria were: (1) other condition than COPD as main diagnosis; (2) unknown or inaccessible FEV_1 and/or FEV_1/FVC; (3) inability to answer CAT questionnaire (e.g. severe dementia, severe cognitive disability).

Definitions

A AECOPD was defined as an acute change of baseline symptoms (dyspnea, cough, and/or sputum production) that is beyond normal day-to-day variation [1].

CAT is a questionnaire that measures the impact of COPD on patient´s health status. It evaluates the following 8 items: cough, dyspnea, sputum production, chest tightness, impairment in daily activities, confidence, quality of sleep and energy. Each item is evaluated from 0 to 5, an higher score meaning greater severity. [21].

Comorbidities were considered concurrent diseases and chronic medical conditions that may affect COPD patients [22].

Data collection

Participants were recruited at the ED admission and prospectively followed up for 30 days. All data was entered in a form specifically designed for the study.

At admission, symptoms were evaluated with CAT. Illiterate and other patients with difficulties in self-administering the CAT were questioned orally. Patients' demographic and clinical data were collected retrospectively based on clinical files and completed with an interview during ED admission. The demographic data included sex, age, education, home, professional and marital status. The clinical data included COPD-related characteristics and a comorbidity check-list. Among COPD-related characteristics, smoker status (non-smoker,

smoker, ex-smoker) and pack-year, FEV_1 and FEV_1/FVC, Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification of severity of airflow limitation and GOLD combined classification, previous year exacerbations and hospitalizations and COPD management context (primary care or hospital care) were registered. Pharmacotherapy and other treatments (oxygen therapy, non-invasive ventilation, pulmonary rehabilitation, flu and pneumococcal vaccination) administered in the previous 12 months were also recorded.

In the follow-up period, the need for hospitalization and the length of hospitalization were recorded. Thirty days after the hospital discharge, a new CAT was performed by telephone interview. Fatality, ED readmissions, new hospitalizations (rehospitalizations) and their respective causes were obtained based on electronic health records and completed with phone interview.

Statistics

Categorical variables were described as number of cases and percentages and compared using the chi-square or Fisher's exact test. Continuous variables as median and standard deviation and compared using the t-test, Mann-Whitney U test or Kruskal-Wallis test, as appropriated. The Spearman's test was used to compare the continuous variables: number of comorbidities, length of hospitalization, CAT at admission, CAT recovery. Additionally, the associations between comorbidities and the study outcomes (hospitalization, ED readmission, rehospitalization, fatal outcome) were assessed using chi-square or Fisher's exact test. The magnitude of the associations with the study outcomes was assessed using logistic regression and presented as odds ratio (OR) and respective 95% confidence intervals (95%CI).

All p-values were two tailed and statistical significance was defined as $p < 0.05$. Statistical analyses were performed using the software STATA® 13.0 (StataCorp, USA).

Results

A total of 115 patients were enrolled in the study**.** Table 1 describes the demographic and clinical characteristics of the patients. Mean age was 71,9±11,7 and 77,4 % were men. 64,4 % patients had at least four years of education and 17,4 % were illiterate. The majority lived with one or more family members (76,5%), 20,9% lived alone and only 3 patients were institutionalized; 84,3% had retired, 63,5% were married and 17,4% were widowed.

A proportion of 61,7% were former smokers and mean packs/year was 55,8±39,0. Mean FEV_1 was 49,2±15,2% predicted and mean FEV_1/FVC was 53,7±10,9. The majority of the patients had either moderate (46,1%) or severe (40%) airflow limitation. The rest of the patients had very severe airway obstruction (13,9%). None had a mild (GOLD 1) airflow limitation. GOLD COPD combined assessment showed that the majority belong to groups with "more symptoms" (group D with 34,8% and group B with 33,9%). Group C accounts for 20,9 % and group A for 10,4% of the patients. In the previous year, 61,7% (N=71) admitted in the ED for AECOPD and 39 of these were hospitalized.

The most common comorbidities were hypertension (64,4%), heart failure (49,6%) and dyslipidemia (47%). Also common are anxiety (35,7%), overweight (33%), gastroesophageal reflux disease (GERD) (32,2%), bronchiectasis (27%), type 2 diabetes mellitus (24,4%), arrhythmias (20%), ischemic heart disease (19,1%) and depression (19,1%). Of the 23 patients with cardiac arrhythmia, 21 had atrial fibrillation (AF). Of the 10 patients with extrapulmonary neoplasia, five had colorectal, two had bladder, two had prostate and one had laryngeal cancer. The mean body mass index (BMI) was 25,0±5,1 kg/m^2. A proportion of 46,1% had normal BMI and only 7 patients were underweight. Overall, 19,1% (N=22) had community-acquired pneumonia (CAP) requiring ED admission in the previous 12 months. Of these, 17 were hospitalized due to CAP in the same period.

Figure 1 shows the burden of comorbidities.

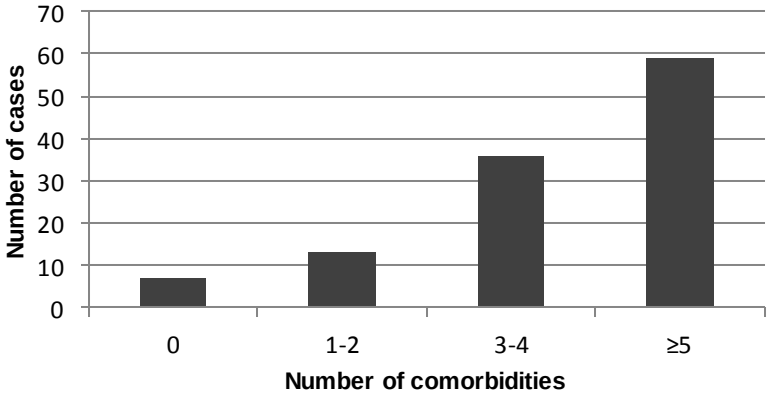

Figure 1: Burden of comorbidities

Table 1: Demographic and clinical characteristics

Demographic Characteristics	
Male	*77,4 (89)*
Age	*71,9 ± 11,7*
Education (years)	
0	*17,4 (20)*
≤4	*64,4 (74)*
>4 ≤6	*0,9 (1)*
>6 ≤9	*13% (15)*
>9 ≤12	*4,4 (5)*
Home Status	
Alone	*20,9 (24)*
Family	*76,5 (88)*
Institution	*2,6 (3)*
Profissional Status	
Employed	*6,1 (7)*
Unemployed	*9,6 (11)*
Retired	*84,3 (97)*
Marital Status	
Single	*7,8 (9)*
Married	*63,5 (73)*
Divorced	*11,3 (13)*
Widowed	*17,4 (20)*
Clinical Characteristics	
COPD related characteristics	
Smoke Status	
Non-smoker	*13 (15)*
Smoker	*25,2 (29)*
Ex-smoker	*61,7 (71)*
Pack-year	*55,8 ± 39,0*
FEV_1	*49,2 ± 15,2*
FEV_1/FVC	*53,7 ± 10,9*
GOLD Classification of Severity of Airflow Limitation	
1	*0 (0)*
2	*46,1 (53)*
3	*40,0 (46)*
4	*13,9 (16)*
GOLD combined COPD assessment	
A	*10,4 (12)*
B	*33,9 (39)*
C	*20,9 (24)*
D	*34,8 (40)*
AECOPD requiring ED admission in the last 12 months	*61,7 (71)*
With hospitalization	*33,9 (39)*
COPD management	
Primary health care	*13,9 (16)*
Hospital care	*86,1 (99)*
Comorbidities	
Respiratory	
Community-acquired pneumonia in the last 12 months	*19,1 (22)*
With hospitalization	*14,7 (17)*
Asthma	*9,6 (11)*
Obstructive Sleep Apnea	*8,7 (10)*
Bronchiectasis	*27,0 (31)*
Risk exposure	*19,1 (22)*
Cardiovascular	
Heart Failure	*49,6 (57)*
Previous acute myocardial infarct	*7,0 (8)*
Ischemic heart disease	*19,1 (22)*
Arrhytmias	*20,0 (23)*
Hypertension	*64,4 (74)*
Peripheric artery disease	*3,5 (4)*
Previous venous thrombosis/Pulmonary thromboembolism	*2,6 (3)*
Previous stroke	*7,0 (8)*

Metabolic	
Body mass index (kg/m²)	*25,0 ± 5,2*
Underweight	*6,1 (7)*
Normal	*46,1 (53)*
Overweight	*33,0 (38)*
Obesity	*14,8 (17)*
Type 2 Diabetes Mellitus	*24,4 (28)*
Dyslipidemia	*47,0 (54)*
Ostheoporosis	*6,1 (7)*
Psychiatric	
Anxiety	*35,7 (41)*
Depression	*19,1 (22)*
Neoplasic	
Pulmonary	*2,6 (3)*
Extra-pulmonary	*8,7 (10)*
Other	
Chronic Kidney Disease	*13,0 (15)*
Chronic Kidney Disease Stages	
1	*13,3 (2)*
2	*6,7 (1)*
3	*46,7 (7)*
4	*26,7 (4)*
5	*6,7 (1)*
Gastroesophageal reflux disease	*32,2 (37)*
Gastritis	*4,4 (5)*
Peptic Ulcer	*0,9 (1)*
Chronic Hepatic Disease	*1,7 (2)*
Benign Prostatate Hypertrophy	*14,6 (13)*
Previous 12 months therapy	
Anticholinergic	
Short-acting	*16,5 (19)*
Long-acting	*54,8 (63)*
B2-agonists	
Short-acting	*18,3 (21)*
Long-acting	*79,1 (91)*
Methylxanthines	*23,5 (27)*
Inhaled corticosteroids	*63,5 (73)*
Systemic costicosteroids	*5,2 (6)*
B-blocker	*33,9 (39)*
Angiotension-convertig enzyme inhibitors	*36,5 (42)*
Angiotensin II receptor blockers	*7,9 (9)*
Calcium channel blocker	*13,9 (16)*
Diuretic	*55,7 (64)*
Statin	*38,3 (44)*
Antiplatelet aggregation agents	*33,0 (38)*
Anticoagulant agents	*10,4 (12)*
Oral antidiabetic agents	*20,0 (23)*
Insulin	*6,1 (7)*
Proton pump inhibitors	*34,8 (40)*
Benzodiazepines	*28,7 (33)*
Antidepressants	*13,0 (15)*
Oxygen therapy	*25,2 (29)*
Non-invasive ventilation	
CPAP	*4,3 (5)*
BPAP	*6,1 (7)*
Pulmonary reabilitation	*10,4 (12)*
Flu vaccionation	*77,4 (89)*
Pneumcoccal vaccination	*45,2 (52)*

Quantitative variables are presented as mean ± standard deviation. Discrete variables are presented as percentage (cases). GOLD - Global Initiative for Chronic Obstructive Lung Disease; FEV_1 *- forced expiratory volume in 1 second;* FEV_1/FVC *- forced expiratory volume in 1 second/forced vital capacity; AECOPD= acute exacerbation od chronic obstructive pulmonary disease; CPAP - Continuous positive airway pressure ; BPAP - Bilevel positive airway pressure*

Hospitalization, 30-day ED readmissions, rehospitalizations and fatality

Almost two thirds (63,5%) of AECOPD patients were hospitalized. The mean length of hospitalization was 11,5±11,1 days. Overall, 30,4% (N=35) were readmitted in the ED due to any cause, 22 of these were hospitalized. Concerning ED readmission cause, 23 were readmitted for AECOPD, nine for acute heart failure and three for infection. The 30-day fatality related to any cause was 3,5% (N=4). All deaths occurred during a subsequent hospitalization.

CAT at ED admission, after 30 days and recovery

CAT at ED admission, at 30-days and their difference (CAT recovery) is shown in table 2. Mean CAT in ED admission was 22,0±6,2 (95% confidence interval(CI)) and at 30 days after hospital discharge was 18,4±6,8 (95% CI). CAT decreased between ED admission for AECOPD and 30 days after discharge. Mean CAT recovery was 3,6±3,7 (95% CI). Moreover, patients whose ED visit determined hospitalization improved 3,9±3,8 CAT points (95% CI), whereas patients who were not hospitalized improved 3,1±3,4 (95% CI).

Among patients that had an ED readmission for any cause, the recovery was less pronounced (2,7±2,3, 95% CI) than among patients that had no additional admissions (4,0±4,1; 95% CI). CAT score recovery also showed differences between patients rehospitalized for any cause (2,3±2,0; 95% CI) and non-rehospitalized (3,9±4,0; 95% CI). Comparing patients who had an ED readmission for AECOPD with those who did not, the first group had a less pronounced recovery on CAT (2,5±2,2; 95% CI versus 3,9±3,9; 95% CI). The same trend was found comparing patients who were rehospitalized for AECOPD and the ones who did not (2,6±2,2; 95% CI versus 3,7±3,8; 95% CI).

Table 2: CAT at ED admission, CAT 30 days after hospital discharge and CAT recovery

		Cases	CAT			P-value
			ED admission	30 days after discharge	Recovery	
Sample		111	22,0 ± 6,2	18,4 ± 6,8	3,6 ± 3,7	*<0,001*
Hospitalization	**Yes**	70	22,4 ± 6,6	18,5 ± 7,2	3,9 ± 3,8	*<0,001*
	No	41	21,3 ± 5,5	18,2 ± 6,2	3,1 ± 3,4	*<0,001*
ED readmission for any cause	**Yes**	34	21,0 ± 5,6	18,2 ± 6,7	2,7 ± 2,3	*<0,001*
	No	77	22,4 ± 6,4	18,4 ± 6,9	4,0 ± 4,1	*<0,001*
ED readmission for AECOPD	**Yes**	22	19,7 ± 4,8	17,2 ± 5,5	2,5 ± 2,2	*<0,001*
	No	89	22,6 ± 6,4	18,7 ± 7,1	3,9 ± 3,9	*<0,001*
Rehospitalization for any cause	**Yes**	22	21,4 ± 6,0	19,0 ± 6,6	2,3 ± 2,0	*<0,001*
	No	89	22,1 ± 6,3	18,2 ± 6,9	3,9 ± 4,0	*<0,001*
Rehospitalization for AECOPD	**Yes**	13	18,8 ± 5,6	16,2 ± 6,3	2,6 ± 2,2	*<0,001*
	No	98	22,4 ± 6,2	18,7 ± 6,9	3,7 ± 3,8	*<0,001*

AECOPD - acute exacerbation of chronic obstructive pulmonary disease; CAT - COPD assessment test

Comorbidities and CAT during ED admission and 30-days CAT recovery

Table 3 shows the relationship between CAT score during ED admission and CAT recovery for each comorbidity. No relationship was found between CAT during ED admission and each comorbidity. An association between CAT recovery and BMI was found (p=0.003). Underweight patients had the worst CAT recovery (1,8±1,2), followed by the obese (2,7±2,4). Compared to their overweight counterparts (5,0±3,6), normal BMI patients had a less pronounced CAT recovery (3,2±4,1). No relationship was found between CAT recovery and other comorbidities.

CAT during ED admission (Spearman's Coefficient = 0,10; p = 0,280) and CAT recovery (Spearman's Coefficient 0,16; p = 0,870) were shown to be independent of the number of comorbidities .

Comorbidities and hospitalization, 30-day ED readmission and rehospitalization and fatality

Table 4 shows the relationship between comorbidities, hospitalization and its length. No comorbidities were positively associated with hospitalization or the length of hospitalization.

Table 5 shows the relationship between comorbidities and ED readmission, for any cause and for AECOPD. Table 6 shows the relationship between comorbidities and rehospitalization for any cause and for AECOPD. No single disease was associated either with ED readmission or rehospitalization for any cause in the subsequent 30 days. GERD was associated with an increased risk of ED readmission for AECOPD at 30 days (OR 2.92; CI95% = (1,14-7,47)) as well as with an increased risk of rehospitalization for AECOPD (OR 3.31; CI95% = (1,06-10,38)). Previous history of stroke was also associated with higher risk of rehospitalization for AECOPD (OR 5.23; CI95% = (1,09-24,95)).

Table 7 shows the association between comorbidities and fatality. An association between previous history of stroke and 30-day fatality was found (p=0.024).

Number of comorbidities and hospitalization, 30-days ED readmission and rehospitalizations

Both hospitalization during ED admission (p=0,479) and the length of hospitalization (Spearman's Coefficient = 0,04; p = 0,690) were shown to be independent of the number of comorbidities. Also, both ED readmissions (p= 0,522) and rehospitalization (p= 0,891) for any cause were shown to be independent of the number of comorbidities.

Table 3: Comparison of CAT at ED admission and 30-days CAT recovery and comorbidities

	CAT at ED admission				CAT recovery			
	Cases	**Mean**	**Standard deviation**	***P-value***	**Cases**	**Mean**	**Standard deviation**	***P-value***
Respiratory								
Community-acquired pneumonia in the last 12 months	*22*	*23,0*	*5,4*	*0,464*	*22*	*3,0*	*4,2*	*0,224*
Asthma	*11*	*24,7*	*4,9*	*0,076*	*11*	*4,1*	*2,6*	*0,200*
Obstructive Sleep Apnea	*10*	*19,7*	*7,6*	*0,366*	*10*	*4,4*	*4,1*	*0,425*
Bronchiectasis	*31*	*21,2*	*6,2*	*0,379*	*31*	*3,5*	*4,2*	*0,725*
Cardiovascular								
Heart Failure	*57*	*22,8*	*5,5*	*0,199*	*55*	*3,5*	*4,0*	*0,553*
Previous acute myocardial infarct	*8*	*23,4*	*7,1*	*0,485*	*7*	*4,3*	*4,8*	*0,913*
Ischemic heart disease	*22*	*21,6*	*5,5*	*0,581*	*21*	*3,6*	*4,9*	*0,328*
Arrhytmias	*23*	*22,1*	*6,2*	*0,737*	*22*	*3,1*	*5,3*	*0,125*
Hypertension	*74*	*22,8*	*5,5*	*0,157*	*71*	*3,8*	*4,1*	*0,595*
Peripheric artery disease	*4*	*25,0*	*6,2*	*0,423*	*3*	*9,0*	*9,5*	*0,190*
Previous venous thrombosis/ Pulmonary thromboembolism	*3*	*29,7*	*6,7*	*0,061*	*3*	*8,0*	*7,9*	*0,248*
Previous stroke	*8*	*23,8*	*6,2*	*0,458*	*6*	*1,5*	*1,5*	*0,057*
Metabolic								
Body mass index								
Underweight	*7*	*23,0*	*5,7*		*6*	*1,8*	*1,2*	
Normal	*53*	*22,1*	*6,0*	*0,959*	*52*	*3,2*	*4,1*	*0,003*
Overweight	*38*	*22,3*	*6,4*		*36*	*5,0*	*3,6*	
Obesity	*17*	*21,8*	*7,1*		*17*	*2,7*	*2,4*	
Type 2 Diabetes Mellitus	*28*	*22,4*	*6,2*	*0,772*	*28*	*3,8*	*3,4*	*0,537*
Dyslipidemia	*54*	*22,4*	*5,8*	*0,728*	*52*	*3,7*	*4,0*	*0,873*
Ostheoporosis	*7*	*22,0*	*3,8*	*0,783*	*7*	*3,9*	*6,6*	*0,903*
Psychiatric								
Anxiety	*41*	*22,3*	*5,4*	*0,944*	*40*	*4,1*	*4,2*	*0,321*
Depression	*22*	*22,3*	*5,6*	*0,926*	*20*	*4,7*	*4,3*	*0,123*
Neoplasic								
Pulmonary	*3*	*24,7*	*3,8*	*0,477*	*2*	*3,0*	*4,2*	*0,807*
Extra-pulmonary	*10*	*23,7*	*7,2*	*0,457*	*9*	*4,3*	*5,3*	*0,931*
Other								
Chronic Kidney Disease	*15*	*23,1*	*6,3*	*0,274*	*15*	*3,4*	*3,7*	*0,904*
Gastroesophageal reflux disease	*37*	*22,5*	*5,0*	*0,871*	*35*	*3,8*	*5,5*	*0,268*
Gastritis	*5*	*21,6*	*3,8*	*0,617*	*5*	*5,0*	*6,8*	*0,820*
Peptic Ulcer	*1*	*22,0*	*NA*	*0,857*	*1*	*6,0*	*NA*	*0,268*
Chronic Hepatic Disease	*2*	*20,0*	*1,4*	*0,410*	*2*	*3,0*	*0,0*	*0,983*
Benign Prostatate Hypertrophy	*13*	*24,2*	*4,1*	*0,170*	*13*	*3,1*	*3,4*	*0,233*

¶ - *logistic-regression analysis; NA – Not applicable; CAT - COPD assessment test*

Table 4: Comparison of comorbidities between hospitalized and non-hospitalized patients and their relationship with the length of hospitalization

	Hospitalization					Length of hospitalization			
	No	Yes		Univariable analysis¶		Cases	Mean	Standard deviation	P-value
	n=42	*n=73*	*P-value*	*OR*	*95% CI*				
Respiratory									
Community-acquired pneumonia in the last 12 months	*7*	*15*	*0,611*	*1,29*	*0,48-3,48*	*22*	*7,73*	*13,04*	*0,873*
Asthma	*2*	*9*	*0,200*	*2,81*	*0,58-13,69*	*11*	*8,55*	*7,12*	*0,199*
Obstructive Sleep Apnea	*3*	*7*	*0,655*	*1,38*	*0,34-5,64*	*10*	*5,80*	*6,43*	*0,972*
Bronchiectasis	*14*	*17*	*0,244*	*0,61*	*0,26-1,41*	*31*	*6,97*	*11,61*	*0,474*
Cardiovascular									
Heart Failure	*16*	*41*	*0,064*	*2,88*	*0,96-4,52*	*57*	*8,05*	*9,99*	*0,175*
Previous acute myocardial infarct	*2*	*6*	*0,483*	*1,79*	*0,34-9,30*	*8*	*6,50*	*7,39*	*0,804*
Ischemic heart disease	*5*	*17*	*0,142*	*2,25*	*0,76-6,62*	*22*	*6,14*	*6,27*	*0,768*
Arrhytmias	*6*	*17*	*0,249*	*1,82*	*0,66-5,05*	*23*	*8,74*	*8,73*	*0,195*
Hypertension	*24*	*50*	*0,223*	*1,63*	*0,74-3,58*	*74*	*7,86*	*9,54*	*0,112*
Peripheric artery disease	*2*	*2*	*0,573*	*0,56*	*0,08-4,15*	*4*	*4,50*	*5,26*	*0,625*
Previous venous thrombosis/ Pulmonary thromboembolism	*2*	*1*	*0,302*	*0,28*	*0,02-3,16*	*3*	*3,67*	*6,35*	*0,488*
Previous stroke	*4*	*4*	*0,417*	*0,55*	*0,13-2,33*	*8*	*7,75*	*9,02*	*0,917*
Metabolic									
Body mass index									
Underweight	*22*	*31*	*0,153*	*0,28*	*0,05-1,60*	*7*	*1,86*	*3,48*	
Normal	*5*	*2*	-----	-----	-----	*53*	*7,36*	*11,64*	*0,123*
Overweight	*11*	*27*	*0,221*	*1,74*	*0,72-4,24*	*38*	*6,53*	*6,32*	
Obesity	*4*	*13*	*0,189*	*2,30*	*0,66-8,02*	*17*	*11,12*	*14,54*	
Type 2 Diabetes Mellitus	*6*	*22*	*0,062*	*2,59*	*0,95-7,02*	*28*	*7,43*	*7,59*	*0,275*
Dyslipidemia	*18*	*36*	*0,504*	*1,30*	*0,60-2,79*	*54*	*6,46*	*7,37*	*0,993*
Ostheoporosis	*4*	*3*	*0,255*	*0,41*	*0,09-1,91*	*7*	*12,57*	*22,20*	*0,739*
Psychiatric									
Anxiety	*15*	*26*	*0,992*	*1,00*	*0,45-2,20*	*41*	*7,24*	*11,57*	*0,991*
Depression	*9*	*13*	*0,635*	*0,80*	*0,31-2,05*	*22*	*7,50*	*14,85*	*0,504*
Neoplasic									
Pulmonary	*2*	*1*	*0,302*	*0,28*	*0,02-3,16*	*3*	*23,33*	*40,41*	*0,779*
Extra-pulmonary	*3*	*7*	*0,655*	*1,38*	*0,34-5,64*	*10*	*8,90*	*7,37*	*0,236*
Other									
Chronic Kidney Disease	*4*	*11*	*0,399*	*1,69*	*0,50-5,67*	*15*	*3,87*	*3,80*	*0,368*
Gastroesophageal reflux disease	*12*	*25*	*0,531*	*1,30*	*0,57-2,97*	*37*	*8,46*	*12,06*	*0,603*
Gastritis	*3*	*2*	*0,282*	*0,37*	*0,06-2,29*	*5*	*16,40*	*26,17*	*0,973*
Peptic Ulcer	*1*	*0*	*NA*	*NA*	*NA*	*1*	*0*	*NA*	*NA*
Chronic Hepatic Disease	*1*	*1*	*0,693*	*0,57*	*0,03-9,35*	*2*	*6,50*	*9,19*	*0,966*
Benign Prostatate Hypertrophy	*7*	*6*	*0,176*	*0,45*	*0,14-1,43*	*13*	*3,92*	*5,71*	*0,177*

¶ - *logistic-regression analysis; OR – Odds Ratio; CI – Confidence Interval*

Table 5: Comparison of comorbidities between ED readmitted and non-readmitted patients for any cause and for AECOPD

	ED Readmission									
	Any cause					AECOPD				
	No	Yes			Univariable analysis¶	No	Yes			Univariable analysis¶
	n=80	*n=35*	*P-value*	*OR*	*95% CI*	*n=92*	*n=23*	*P-value*	*OR*	*95% CI*
Respiratory										
Community-acquired pneumonia in the last 12 months	*16*	*61*	*0,720*	*0,83*	*0,29-2,33*	*19*	*3*	*0,411*	*0,58*	*0,15-2,15*
Asthma	*8*	*3*	*0,811*	*0,84*	*0,21-3,39*	*10*	*1*	*0,359*	*0,37*	*0,05-3,07*
Obstructive Sleep Apnea	*6*	*4*	*0,494*	*1,60*	*0,42-6,03*	*7*	*3*	*0,414*	*1,82*	*0,43-7,67*
Bronchiectasis	*20*	*11*	*0,476*	*1,38*	*0,57-3,30*	*26*	*5*	*0,530*	*0,71*	*0,24-2,10*
Cardiovascular										
Heart Failure	*42*	*15*	*0,342*	*0,68*	*0,30-1,51*	*47*	*10*	*0,515*	*0,74*	*0,29-1,85*
Previous acute myocardial infarct	*8*	*0*	*NA*	*NA*	*NA*	*8*	*0*	*NA*	*NA*	*NA*
Ischemic heart disease	*18*	*4*	*0,173*	*0,44*	*0,14-1,43*	*19*	*3*	*0,411*	*0,58*	*0,15-2,15*
Arrhytmias	*17*	*6*	*0,613*	*0,77*	*0,27-2,15*	*19*	*4*	*0,727*	*0,81*	*0,25-2,66*
Hypertension	*54*	*20*	*0,288*	*0,64*	*0,28-1,45*	*61*	*23*	*0,383*	*0,66*	*0,26-1,68*
Peripheric artery disease	*2*	*2*	*0,400*	*2,36*	*0,32-17,50*	*3*	*1*	*0,800*	*1,35*	*0,13-13,60*
Previous venous thrombosis/Pulmonary thromboembolism	*3*	*0*	*NA*	*NA*	*NA*	*3*	*0*	*NA*	*NA*	*NA*
Previous stroke	*4*	*4*	*0,225*	*2,45*	*0,58-10,43*	*5*	*3*	*0,214*	*2,61*	*0,58-11,83*
Metabolic										
Body mass index										
Underweight	*37*	*16*	*0,170*	*3,08*	*0,62-15,39*	*41*	*12*	*0,258*	*2,56*	*0,50-13,07*
Normal	*3*	*4*	-----	-----	-----	*4*	*3*	-----	-----	-----
Overweight	*27*	*11*	*0,898*	*0,94*	*0,37-2,35*	*31*	*7*	*0,626*	*0,77*	*0,27-2,19*
Obesity	*13*	*4*	*0,595*	*0,71*	*0,20-2,52*	*16*	*1*	*0,154*	*0,21*	*0,03-1,78*
Type 2 Diabetes Mellitus	*18*	*10*	*0,486*	*1,38*	*0,56-3,40*	*22*	*6*	*0,828*	*1,12*	*0,39-3,20*
Dyslipidemia	*38*	*16*	*0,860*	*0,93*	*0,42-2,06*	*43*	*11*	*0,926*	*1,04*	*0,42-2,61*
Ostheoporosis	*6*	*1*	*0,357*	*0,36*	*0,04-3,13*	*6*	*1*	*0,699*	*0,65*	*0,07-5,69*
Psychiatric										
Anxiety	*31*	*10*	*0,296*	*0,63*	*0,27-1,50*	*36*	*5*	*0,126*	*0,43*	*0,15-1,27*
Depression	*14*	*8*	*0,503*	*1,40*	*0,53-3,71*	*18*	*4*	*0,813*	*0,87*	*0,26-2,86*
Neoplasic										
Pulmonary	*2*	*1*	*0,912*	*1,15*	*0,10-13,08*	*2*	*1*	*0,566*	*2,05*	*0,18-23,59*
Extra-pulmonary	*9*	*1*	*0,174*	*0,23*	*0,03-1,91*	*9*	*1*	*0,421*	*0,42*	*0,05-3,49*
Other										
Chronic Kidney Disease	*10*	*5*	*0,794*	*1,17*	*0,37-3,71*	*11*	*4*	*0,491*	*1,55*	*0,44-5,40*
Gastroesophageal reflux disease	*22*	*15*	*0,107*	*1,98*	*0,86-4,53*	*25*	*12*	*0,025*	*2,92*	*1,14-7,47*
Gastritis	*3*	*2*	*0,637*	*1,56*	*0,25-9,75*	*3*	*2*	*0,272*	*2,83*	*0,44-17,99*
Peptic Ulcer	*1*	*0*	*NA*	*NA*	*NA*	*1*	*0*	*NA*	*NA*	*NA*
Chronic Hepatic Disease	*2*	*0*	*NA*	*NA*	*NA*	*2*	*0*	*NA*	*NA*	*NA*
Benign Prostatate Hypertrophy	*11*	*2*	*0,225*	*0,38*	*0,08-1,81*	*12*	*1*	*0,264*	*0,30*	*0,37-2,46*

¶ - logistic-regression analysis; AECOPD - acute exacerbation of chronic obstructive pulmonary disease; OR – Odds Ratio; CI – Confidence Interval; NA – Not applicable

Table 6: Comparison of comorbidities between rehospitalized and non-rehospitalized patients for any cause and for AECOPD

	Rehospitalization									
	Any cause					AECOPD				
	No	Yes		Univariable analysis¶		No	Yes		Univariable analysis¶	
	n=93	*n=22*	*P-value*	*OR*	*95% CI*	*N=101*	*n=14*	*P-value*	*OR*	*95% CI*
Respiratory										
Community-acquired pneumonia in the last 12 months	*18*	*4*	*0,900*	0,93	0,28-3,07	*21*	*1*	*0,250*	0,29	0,04-2,37
Asthma	*9*	*2*	*0,933*	0,93	0,19-4,66	*11*	*0*	*NA*	NA	NA
Obstructive Sleep Apnea	*8*	*2*	*0,942*	1,06	0,21-5,40	*8*	*2*	*0,435*	1,94	0,37-10,21
Bronchiectasis	*24*	*7*	*0,569*	1,34	0,49-3,68	*27*	*4*	*0,885*	1,10	0,32-3,80
Cardiovascular										
Heart Failure	*47*	*10*	*0,668*	0,82	0,32-2,07	*51*	*6*	*0,593*	0,74	0,24-2,27
Previous acute myocardial infarct	*8*	*0*	*NA*	NA	NA	*8*	*0*	*NA*	NA	NA
Ischemic heart disease	*19*	*3*	*0,470*	0,61	0,16-2,30	*19*	*3*	*0,816*	1,18	0,30-4,64
Arrhytmias	*18*	*5*	*0,722*	1,23	0,40-3,76	*20*	*3*	*0,887*	1,11	0,28-4,33
Hypertension	*62*	*12*	*0,289*	0,6	0,23-1,54	*65*	*9*	*0,996*	1,00	0,31-3,20
Peripheric artery disease	*3*	*1*	*0,762*	1,43	0,14-14,42	*3*	*1*	*0,439*	2,51	0,24-25,98
Previous venous thrombosis/Pulmonary thromboembolism	*3*	*0*	*NA*	NA	NA	*3*	*0*	*NA*	NA	NA
Previous stroke	*5*	*3*	*0,186*	2,78	0,61-12,64	*5*	*3*	*0,038*	5,24	1,10-24,95
Metabolic										
Body mass index										
Underweight	*42*	*11*	*0,639*	*1,53*	0,26-8,96	*46*	*7*	*0,299*	2,63	0,42-16,26
Normal	*5*	*2*	-----	-----	-----	*5*	*2*	-----	-----	-----
Overweight	*30*	*8*	*0,972*	*1,02*	0,37-2,84	*33*	*5*	*0,994*	1,00	0,29-3,41
Obesity	*16*	*1*	*0,187*	*0,24*	0,03-2,00	*17*	*0*	*NA*	NA	NA
Type 2 Diabetes Mellitus	*21*	*7*	*0,367*	1,60	0,58-4,44	*23*	*5*	*0,296*	1,88	0,57-6,18
Dyslipidemia	*45*	*9*	*0,528*	0,74	0,29-1,89	*46*	*8*	*0,418*	1,59	0,52-4,93
Ostheoporosis	*6*	*1*	*0,738*	0,69	0,08-6,05	*6*	*1*	*0,860*	1,22	0,14-10,94
Psychiatric										
Anxiety	*33*	*8*	*0,938*	1,04	0,40-2,73	*37*	*4*	*0,557*	0,69	0,20-2,36
Depression	*17*	*5*	*0,634*	1,31	0,43-4,06	*19*	*3*	*0,816*	1,18	0,30-4,64
Neoplasic										
Pulmonary	*2*	*1*	*0,536*	2,17	0,19-25,03	*2*	*1*	*0,289*	3,81	0,32-44,98
Extra-pulmonary	*9*	*1*	*0,454*	0,44	0,05-3,70	*9*	*1*	*0,826*	0,79	0,09-6,72
Other										
Chronic Kidney Disease	*10*	*5*	*0,143*	2,44	0,74-8,05	*11*	*4*	*0,078*	3,27	0,88-12,22
Gastroesophageal reflux disease	*27*	*10*	*0,143*	2,04	0,79-5,27	*29*	*8*	*0,040*	3,31	1,06-10,38
Gastritis	*3*	*2*	*0,245*	3,00	0,47-19,15	*3*	*2*	*0,078*	5,44	0,83-35.93
Peptic Ulcer	*1*	*0*	*NA*	NA	NA	*1*	*0*	*NA*	NA	NA
Chronic Hepatic Disease	*2*	*0*	*NA*	NA	NA	*2*	*0*	*NA*	NA	NA
Benign Prostatate Hypertrophy	*11*	*2*	*0,716*	0,75	0,15-3,63	*12*	*1*	*0,604*	0,57	0,07-4,76

¶ - logistic-regression analysis; AECOPD - acute exacerbation of chronic obstructive pulmonary disease; OR – Odds Ratio; CI – Confidence Interval ; NA – Not applicable

Table 7: Comparison of comorbidities and fatal outcome

	Fatal outcome		
	No	**Yes**	***P-value***
	n=111	***n=4***	
Respiratory			
Community-acquired pneumonia in the last 12 months	*22*	*0*	*NA*
Asthma	*11*	*0*	*NA*
Obstructive Sleep Apnea	*10*	*0*	*NA*
Bronchiectasis	*31*	*0*	*NA*
Cardiovascular			
Heart Failure	*55*	*2*	*0,684*
Previous acute myocardial infarct	*7*	*1*	*0,254*
Ischemic heart disease	*21*	*1*	*0,578*
Arrhytmias	*22*	*1*	*0,596*
Hypertension	*71*	*3*	*0,551*
Peripheric artery disease	*4*	*0*	*NA*
Previous venous thrombosis/Pulmonary thromboembolism	*3*	*0*	*NA*
Previous stroke	*6*	*2*	*0,024*
Metabolic			
Body mass index			
Underweight	*6*	*1*	
Normal	*52*	*1*	*0,253*
Overweight	*36*	*2*	
Obesity	*17*	*0*	
Type 2 Diabetes Mellitus	*28*	*0*	*NA*
Dyslipidemia	*52*	*2*	*0,643*
Ostheoporosis	*7*	*0*	*NA*
Psychiatric			
Anxiety	*40*	*1*	*0,551*
Depression	*20*	*2*	*0,165*
Neoplasic			
Pulmonary	*2*	*1*	*0,102*
Extra-pulmonary	*9*	*1*	*0,309*
Other			
Chronic Kidney Disease	*15*	*0*	*NA*
Gastroesophageal reflux disease	*35*	*2*	*0,593*
Gastritis	*5*	*0*	*NA*
Peptic Ulcer	*1*	*0*	*NA*
Chronic Hepatic Disease	*2*	*0*	*NA*
Benign Prostatate Hypertrophy	*13*	*0*	*NA*

NA – Not applicable

Discussion

In this study, the relevance of comorbidities in patients admitted for AECOPD is emphasized. Cardiovascular, metabolic and psychiatric diseases along with GERD are very prevalent conditions and show the importance in the course of COPD. Hypertension (64,4%) is a major diagnosis among COPD patients, accounting for a reported prevalence of 40-60% throughout the literature [23] [24]. Ischemic heart disease (19,1%) and an history of myocardial infarction (MI) (7%) have higher prevalence than in other studies. In these, the prevalence of ischemic heart disease was reported to be 9% [25], angina 6,6% and acute MI 2,3% [24]. The same trend was found in a Portuguese study, where a prevalence of 18% was reported [26]. This may represent a singularity of the Portuguese COPD population.

Hypertension and ischemic heart disease are the most common causes of heart failure. Heart failure is more prevalent than in other studies [27] [28]. A prevalence of 7% [25] to 25% in patients with COPD aged ≥65 years [28] was described. However, due to overlapping signs and symptoms, 80% of heart failure cases in COPD elderly patients are unrecognized [28].
The prevalence of arrhythmias is also higher than reported (20% vs 12-14%) [29] [30]. The same Portuguese study also showed a higher prevalence (18%), which may also represent a singularity of the Portuguese population. The majority of the arrhythmias are AF [2].

Metabolic comorbidities are also relevant. Dyslipidemia (47% vs 9-51% [31] [2]) and type 2 diabetes mellitus (24,4% vs 11-25% [32] [33]) prevalences are consistent with published data. Obesity (14,8% vs 18%-24,6% [34] [35]) and underweight are less prevalent compared to other studies (6,1% vs 11.7% [36]). The same trend was found for ostheoporosis (6,1% vs 23%) [37] which may be related to underdiagnosis. The prevalence of chronic kidney disease (CKD) is lower than the 22% reported [38].

The risk of cardiovascular disease is increased in COPD patients due to several reasons. Smoking is a leading risk factor for both COPD and ischemic heart disease [39]. Moreover, FEV_1 is a significant risk factor for cardiovascular morbidity and mortality, independent of smoking [40]. Individuals with reduced FEV_1 are at increased risk of atherosclerosis [41]. COPD patients show accelerated degradation of elastin and increased deposition of collagen leading to increased arterial stiffness. This could play a role in the pathogenesis of hypertension [42]. Arrhythmias, especially AF, often reflect the presence of ischemic heart disease and/or hypertension and are more common as airflow limitation worsens [43].

Metabolic comorbidities are related to cardiovascular disease as they represent additional risk factors. Type 2 diabetes mellitus, dyslipidemia and obesity share common mechanisms in COPD, namely central obesity, reduced physical activity, increase smoking,

corticosteroids use and disease-related inflammation and oxidative stress [44]. BMI and diabetes are significantly associated with CKD [45].

Anxiety and depression are important comorbidities that often coexist [46]. The reported prevalences for both diseases are wide, ranging from 7% to 80% for depression [47] [48] and from 6% to 74% for anxiety [48]. This is probably due to heterogeneity in diagnostic criteria. The risk factors for anxiety or depression in COPD patients include severe dyspnea, poor health-related quality of life, impairment of physical functioning, long-term oxygen therapy, acute exacerbations, limited airflow reversibility, living alone, unsupportive families, low BMI and medical comorbidities [49].

GERD reported prevalence ranges between 30-60% in COPD patients [50]. Several mechanisms link GERD to COPD. Firstly, symptoms of GERD are more common with increased intra-abdominal pressure, such as coughing, obesity [51] and hyperinflation of the lungs where the diaphragm is displaced caudally [52]. Secondly, acidification of the lower esophagus increases cough responsiveness in patients with chronic cough [53], and worsens airway hyperreactivity [54]. Thirdly, the autonomic dysfunction often found in COPD patients can lead to impaired lower esophageal sphincter tone and delayed gastric emptying [55]. Moreover, salbutamol at higher dose reduce LOS tone [56].

Theoretically, the risk of cerebrovascular events and the prevalence of peripheral arterial disease (PAD) are increased in COPD patients due to the same reasons mentioned above for cardiovascular diseases. However, previous history of stroke (7%) has a lower prevalence than reported: 7% vs 9,9% [57] for stroke and 14 % [50] for any cerebrovascular event in COPD. The prevalence of cerebrovascular accidents in Portugal varies from 8-2,1% [58] [59]. For this reason, this data is difficult to interpret. The prevalence of PAD in Portugal is 5,9% [60]which is higher than the prevalence found. These differences may be related to the specific population of the present studyand to underdiagnosis.

The prevalences for asthma (9,6%) and obstructive sleep apnea (OSA) (8,7%) are not consistent with the published data. Reported prevalence of asthma among elderly patients with COPD can be as high as 40% [2]. The prevalence of OSA in COPD is not higher than in the general population (around 5%) [2]. The increased risk of neoplastic disorders among COPD patients is believed to be due to a common major risk factor: smoking [61]. Of the 10 patients found to have an extrapulmonary neoplasm, 8 had a smoking-related cancer, namely colorectal cancer, bladder cancer and laryngeal cancer.

The majority of the AECOPD patients that present to ED are hospitalized and mean length of hospitalization (11,5) is higher than expected. The mean of days of hospitalization was 8,2 and 7,0 in 2006 and 2010 respectively [62]. This may be due to an increased rate of complications during the hospitalization inherent to disease or comorbidities severity.

Compared to other studies, the ED readmission rate for any cause and for AECOPD is higher. In a study, a readmission rate of 9,2% at 30 days and 20,3% at 90 days following an admission for AECOPD was reported. In a north-american analysis of 2008, the 30-day all-cause rehospitalization rate after a COPD admission was 20,5%, with 7,1% readmitted primarily for COPD [17]. A follow-up analysis of the same database for 2010 found a similar 30-day readmission rate of 20.9% [18] [63]. This disparity may be related to differences concerning patient characteristics, namely comorbidities and their severity and insufficient disease control as well as other factors related to supportive care after hospital discharge.

In another study, three months after an admission for AECOPD, 20,2% of the patients were readmitted for COPD, 22% for heart failure, 18% for infection and 10% for ischemic heart disease. [64]. This study shows similar causes for readmission, in the same order of prevalence: AECOPD, heart failure and infection

The high rate of readmissions for heart failure supports the fact that heart failure and COPD have common pathways that cause mutual disease progression apart from the systemic effects of smoking and inflammation, such as the renin-angiotensin system overactivation which negatively affects systemic and pulmonary circulation through vasoconstriction; the sympathic system overactivity, which is harmful for the cardiovascular system, can be increased in more severe COPD; and, at a late stage, both diseases share the same type of metabolic modulation, increasing the lipid metabolism, resulting in cachexia [65]. The data supports the fact that an AECOPD may be able to induce a heart failure decompensation, which demonstrates the close interaction between both entities. Despite the higher rate of readmissions compared to other studies, none of the patients died during the index ED admission, which contrasts with other studies that reported a mortality of 7,4% [66] and of 8,5 at 30 days [67].

Other studies reported that CAT is statically different in AECOPD and in the stable state [21] [16] [68]. CAT shows responsiveness to AECOPD treatment. The CAT score during the ED admission is similar to other studies, ranging from 21,4±7,7 [14] to 22,8±4,9 [17]. CAT score at 30 days after hospital discharge (18,4±6,8) is also comparable to a study that uses the same period of follow-up (19,9±7,7) [14]. Two other studies, in which the follow-up period was 6 weeks and 12 weeks, showed a CAT score after follow-up respectively of 15,6±4,5 (CAT score pre-AECOPD treatment 22,8±4,9) [17] and 12,1±5,9 (CAT score pre-AECOPD treatment 22,0±7,0) [18]. CAT recovery (3,6±3,7) is significantly different from the one reported in a study with the same follow-up period (1,4±5,3, p=0,03) [14]. However, it varies significantly and in a non-proportional manner according to the follow-up periods: at 12 weeks the CAT recovery was 6,5±3,9 (p=0,001) in one study [17] and at 6 weeks 9,9±5,1 (p=0,001) in another [18].

Hospitalized patients have a slightly better CAT recovery. This is probably due to the better clinical monitoring and care, not only for the AECOPD but also for comorbidities. It may also represent an increase in self-confidence among patients who were more closely monitored.

ED readmitted and rehospitalized patients for any cause and for AECOPD have a worse CAT recovery compared to non-readmitted or rehospitalized patients. This suggests that CAT is able to detect disturbances in the clinical state of the patient related not only to COPD but also to other clinical entities that negatively affect AECOPD recovery.

A study reported a difference in CAT related with BMI [69]. In the present study no association between CAT during ED admission and BMI is found; however, BMI is associated with CAT recovery. Underweight patients show the worst CAT recovery, probably due to the fact that this group of patients have a more severe disease and less responsive to treatment. Low BMI was previously associated with poor prognosis in stable and exacerbated COPD patients [70]. Obese patients also show worse CAT recovery compared to other groups that may be related to associated cardiovascular and metabolic comorbidities. However, overweight patients recover better than the normal BMI patients. This fact is likely the result of the protective role of the excess weight. This phenomenon, known as “obesity paradox”, is not unique in COPD - and in this case may be called the “overweight paradox”. A possible explanation is that obesity (or overweight, in this case) may be a protective factor in advanced COPD patients, when loss of fat-free mass is an important short-term risk factor for poor outcomes; on the other hand, in earlier stages of COPD, obesity-related conditions such as inflammation and metabolic syndrome are harmful long-term effects [70]. A study showed significant difference on the CAT score recovery at 6 weeks between patients with depressive symptoms (7,0, p=0,012) and those without (11,0, p=0,012) [19]. This is not found in this study.

CAT during ED admission and CAT recovery are independent of the number of comorbidities. The same result was reported in other studies, where the comorbidity burden was classified according to the presence of 0, 1-2 or>=3 diseases [68] [69].

The association of GERD and ED readmission rate for AECOPD at 30 days underlines the relevance of this comorbidity in the course of COPD. Several studies reported the association between GERD symptoms and frequency of AECOPD [71] [72] [73]. In this study, this association may reflect the negative influence of GERD on AECOPD recovery by increasing the risk of therapeutic ineffectiveness. This is supported by the fact that GERD is not associated with ED readmissions for all causes, but only with ED readmission due to AECOPD. Moreover, GERD is also associated with rehospitalizations for AECOPD. This may reflect the severity of the AECOPD relapses in patients with this comorbidity. However, GERD is not associated with hospitalization or with the length of hospitalization during the first ED admission.

Despite the relevance of cerebrovascular disease, there is limited data on impact on COPD [2]. Previous history of stroke is associated with rehospitalization for AECOPD at 30 days. Patients with past history of stroke are likely to have dysphagia, increasing the risk of aspiration, pneumonia and disability. [74]. COPD patients with past history of stroke had higher

risk of aspiration than stroke patients without COPD [75]. This increased risk of aspiration may be responsible for the increased risk of rehospitalization for AECOPD.

A study evaluated hospital mortality, length of hospital stay, 90 days readmission rate and mortality after an admission for AECOPD. The burden of comorbidities was associated with worse outcomes for all four measures. In-hospital mortality risk was increased with cor pulmonale, left ventricular failure, neurological conditions and non-respiratory malignancies whilst 90 day death was also increased in patients with lung cancer or arrhythmias. Ischemic and other heart diseases were important factors in the readmission rate [76]. In this study, specific comorbidities are not associated with hospitalization at ED admission or with the length of hospitalization. Furthermore, heart diseases are not associated with readmissions. On the other hand, the association between 30-day fatality and previous history of stroke may reflect the importance of neurological diseases. The lack of association between specific comorbidities and fatality may be due to the low fatality rate. There is also a lack of association between the number of comorbidities and length of hospitalization, ED readmission or rehospitalizations. This result may reflect the influence of other factors such as COPD severity, comorbidities, treatments performed before the ED admission, ED treatment strategies for AECOPD and complications during the hospitalization. It is also possible that the sample was too small to find other relationships. Finally, a small variability and the finding of clusters of comorbidities compromise the statistical analysis.

Conclusion

This study confirms the high prevalence of comorbidities in ED admitted patients for AECOPD. AECOPD is associated with a high rate of hospitalization and length of hospitalization, and a high rate of ED readmissions and rehospitalizations at 30 days. The analysis of readmission causes also shows the interaction between COPD and other important comorbidity: heart failure. The presence of GERD and/or past history of stroke modify ED readmission and rehospitalization rates; this, may be through the same pathophysiological mechanism – the aspiration of particles. The presence of cerebrovascular diseases worsens 30-day fatality. CAT shows to be an excellent tool to evaluate AECOPD recovery as it is responsive to improvement and sensitive for AECOPD relapses and other clinical entities that affect patient recovery. BMI showed to be relevant concerning CAT recovery.

The severity of COPD and comorbidities, the therapies performed before the ED admission, ED treatment strategies for AECOPD and comorbidities, and complications that intervene during the hospitalization may play a role that needs to be taken into account.

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